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(54) Title: ADHESIVE-COATED SHEET MATERIAL INCORPORATING ANTI-BACTERIAL SUBSTANCES

(57) Abstract

Adhesive-coated liquid-impervious moisture-vapour-permeable thin polymer sheet suitable as a wound covering has an antibacterial, preferably a solid such as silver sulphadiazine, disseminated throughout the adhesive layer, usually in amounts up to 15 wt.%, to provide uniform antibacterial properties over the wound and surrounding skin areas.

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"ADHESIVE-COATED SHEET MATERIAL INCORPORATING ANTI-BACTERIAL SUBSTANCES"

This invention relates to sheet material used for medical purposes.

More especially this invention relates to polymeric sheet material of high moisture vapour permeability having upon one surface a layer of adhesive material which does not destroy the said permeability.

Such material is already known per se and is described in British Patent No. 1 280 631 in general terms. It is available, for example, under the Registered Trade Mark "Op-Site". It is used as a surgical and dressing material to cover wounds (including burns) and surgical sites. In this manner it is effective to keep bacteria from the wound, and to prevent scab formation and inhibit scarring since the layer, while permeable to moisture vapour, obviously slows down the drying time of the wound.

Such material is commonly made of polyurethane sheet, e.g. Goodrich polyether polyurethane sold under the Trade Name "Estane", which can be up to three thousandths of an inch (75 microns) in thickness but is commonly less than 45 microns e.g. about 30 microns. It is coated on one surface with a continuous or discontinuous layer of suitable adhesive to approximately the same thickness. By continuous we mean that the

adhesive covers the whole surface without any gaps or blank spaces; by discontinuous we mean that there is a microporous adhesive, or a pattern of lines or dots of adhesive, the pattern covering the whole surface uniformly but of course leaving occasional gaps between units of adhesive. Both of these expedients are well known in the coating art, but continuous adhesive is preferred in this context to plug any small pinholes in the sheet.

Although a sheet of material as described is effective in keeping from the wound or surgical site airborne bacteria, there remains the problem of any bacteria which happen to be present in the site or, more commonly, upon the surrounding skin. In the enclosed conditions provided by such a sheet, such bacteria can multiply unduly and lead to an infection problem.

It has been proposed to overcome this by liberal application of bacteriocidal or bacteriostatic cream or like formulation over and around the wound or surgical site. There are, however, disadvantages in this procedure since the film, if subsequently applied over this moist cream base layer, can corrugate with movement of the body and generally does not adhere.

The present invention is based upon the realisation that a bacteriostatic or bacteriocidal material

can be incorporated into the adhesive layer of the sheet.

The invention accordingly consists in an adhesive-coated sheet material which is liquid-impervious but has a high moisture-vapour permeability whereby it is suitable as a wound or burn dressing, or surgical drape or like wound-covering material, wherein the adhesive coating has dissiminated throughout its mass an amount of an antibacterial material sufficient to kill bacteria in the wound and surrounding covered skin area.

As well as preserving adhesion and avoiding corrugation, this invention has two advantages. Firstly, the antibacterial substance being disseminated throughout the adhesive is present in uniform known amount per unit area both over the wound and over its surroundings. Secondly, no additional substrate is needed so that the sheet can be accurately emplaced on the skin. As already stated, it then lies flat on the skin with consequent uniform water vapour transmission and bacterial barrier properties. Also avoidance of corrugations allows retention of protective and healing would exudate over burns.

The antibacterial materials could be bacteriostatic but are usually bactericidal in nature. Various types of such materials could be used eg:

(i) metal salts, or like compounds with antibacterial metal ions, e.g. copper, mercury or silver, and optionally with additional nonmetallic ions of antibacterial properties.

(ii) typical antibiotics e.g. neomycin, soframycin, bacitracin, polymycin.

(iii) antibacterials such as chlorhexidine and its salts

(iv) quarternary ammonium compounds e.g. centrimide, domiphen bromide, polymeric quaternaries, and

(v) iodophors such as povidone iodine.

The above compounds are in some instances solid materials, and in some instances liquids: moreover, some can be presented in either form. It is much preferred, however, for solid and finely divided materials to be used.

Again, some of the finely divided solids rely on the presence and activity of a relatively small atom or group such as a metal, othere rely on the presence and activity of a large ionised group, and others again on both. Those utilizing metal ions are most preferable, especially if in combination with another active group.

Most preferred of all for incorporation into the adhesive layer is silver sulphadiazine in finely divided form.

We have found that up to 25%(by weight of adhesive) of the antibacterial, but more preferably up to 15% by weight can be used. The lower limit can be as low as

1% but is prefetably 5% for effective antibacterial properties.

If a dispersed material, such as silver sulphadiazine, is used it is generally a so called "micronised" material. In this the state of subdivision of the material is generally speaking such that 99% of the particles are less than 20 microns in diameter and 90% less than 10 microns. In practice the majority of the particles are less, and usually considerably less, than 5 microns in diameter and are usually completely embedded in the adhesive layer. It is of no disadvantage however if some of the particles project from the adhesive layer since their antibacteral activity is thereby immediately exerted. Indeed, some particles might even bridge the layer from the outside adhesive surface to the polymer.

Although the invention as claimed is not to be construed as relying upon any hypothesis as to the mode of action, it can reasonably be inferred that some solid particles are embedded well within the adhesive coating thickness while others lie near the surface from which(depending on the relative properties of the adhesive and particles), they may protrude as such or may be separated by a thin film of polymer. Thus, when the wound-covering is applied the immediately available surface particles act forthwith to yield up their

antibacterial content, whether or not this is in the form of large ions or small ions, but after this the process is conceivably controlled by ionic diffusion through the adhesive thickness in which the smaller (e.g. metal) ions are more effective. In addition to this, over the mobile and wet wound itself, as distinct from the surrounding more or less stationary and static skin, conditions may be to plasticize the adhesive layer and improve migration of the antibacterial.

Whatever the reasoning the results are not predictable in detail, some antibacterials giving less effective results than might have been expected and others more effective results. In particular silver sulphadiazine, notwithstanding its dissemination throughout a water-insoluble adhesive and its own innate water-insolubility gives interesting and valuable results.

As before, the polymer sheet is preferably polyurethane and and can be up to 75 microns in thickness. More preferably it is 40 microns or less, for example about 30 microns.

The adhesive is usually a polyvinyl ether but is possibly an acrylic adhesive and can also be up to 75 microns in thickness, but is preferably less than 40 microns and usually about 30 microns in thickness.

In the field of medical products high specifications of uniformity, safety, non-toxicity and comfort

must be met. The preferred products of the invention have been assessed in various respects, as itemized below, and found to be improved or not significantly deteriorated.

Thus, for example, it was found that even keeping the total adhesive weight (gms/sq.metre) more or less uniform at different silver sulphadiazine loadings the resultant changes in thickness and uniformity were still within acceptable limits. Also, even after ethylene oxide sterilization, and optionally forced aging, or gamma-irradiation the permeability of these dressings at different percentage loadings of silver sulphadiazine to water vapours, oxygen or carbon dioxide was not significantly changed. Similar results were obtained for tensile and elastic tests, that is to say, no significant differences. Adhesive properties differed slightly after gamma-irradiation for sterilising, but this is an effect on the adhesive (rather than due to the incorporation of silver sulphadiazine) and in any case is not in respect of the adhesion to moist skin.

One area of slight difference is in light-fastness. The sterilization procedures mentioned above can cause some slight discoloration, but not enough to render the film opaque so that the wound cannot be observed. This is probably a consequence of the use of a silver salt, although the film itself is known to discolour upon

exposure to sunlight. Nonetheless, rapid stock turnover minimises this problem.

The invention will be further described with reference to the following Examples.

Example 1.

The adhesive formulation was made up as follows, to a solid content of 59%:

	g
Bakelite EHBM	134.5
Bakelite EHBC	58.8
Kelrez 42463	24.0
Nonox WSL (antioxidant)	1.4
Toluene	53.8
SBP 2	96.9

(standard Petroleum spirit)

Bakelite Resin EHBM is a poly (vinyl ethyl ether) high viscosity resin having 25% non-volatiles in hexane, a reduced viscosity at 20°C. of 4.0 ± 0.5; a plasticity of 1.6 to 2.0 m.m; a flash point $\angle$ 20°F; a specific gravity of 0.7299 and a weight per gallon of 6.07 lbs.

Bakelite Resin EDBC is a poly (vinyl ethyl ether) low viscosity resin having 98% non-volatiles; a reduced viscosity of 20°C. of 0.3 ± 0.1; and a specific gravity at 20°C. of 0.973.

Kelrex ZR142 is a zinc resinate formed by the interaction of zinc oxides with the resin acids in partially dimerised Colophony, contains 9.6% zinc and has a melting point of 160 to 165°C.

Into the above formulation was incorporated 1% of silver sulphadiazine, which is, on a dry basis, 590 milligrams per 100 grams of the mass.

The resulting adhesive was knife-spread on to the 25-micron polyurethane film and was thereafter air-dried for two hours at ambient temperature. A disc of the adhesive-coated film incorporating the silver sulphadiazine, 17 millimetres in diameter was cut and placed adhesive side down on to neomycin assay agar plates pre-seeded with either Bacillus subtilis or Pseudomonas aeruginosa. The plates were left at room temperature for approximately half an hour and then incubated overnight at the optimum temperature for growth. After incubation the zones of inhibited growth around the discs were measured. In each case there was a halo of destruction of the bacteria around the edges of the disc.

Example 2.

The above experiment was repeated except that 10% by weight of the silver sulphadiazine was incorporated into the adhesive. The results, using the same-sized discs as in Example 1, were (for Bacillus subtilis) a 34-millimetre diameter zone of inhibition and (for Pseudomonas aeruginosa) a 28.9 millimetre diameter zone, in each case including the diameter of the disc.

Example 3.

A comparative test was carried out on surgical drape samples containing zero (control) 5% and 10% by weight

(nominal) of silver sulphadiazine (SSD) in the adhesive, as follows :

	S3 Control	Nominal 5% SSD	Nominal 10% SSD
	Pts.by wt.	Pts.by wt.	Pts.by wt.
Bakelite EHBM	36.4	36.4	36.4
Bakelite EHBC	15.9	15.9	15.9
Kelrez 42463	6.5	6.5	6.5
Nonox WSL	0.4	0.4	0.4
Toluene	14.6	14.6	14.6
SBP 2	26.2	26.2	26.2
S.S.D.	NIL	1.5	3.0

The solids content of the adhesive prior to spending is 30%. Thus, each sample contained 100g of solution (30 gms solids) plus the additional SSD content. Therefore, the nominal 5% sample contained 4.8 wt.% SSD and the nominal 10% sample contained 9.1 wt.% SSD.

1 Kg weights of masses were made by the following procedure :

1. Toluene and S.S.D. powder were mixed at high speed for 5 minutes.
2. The speed was reduced to slow and Kelrez and Nonox added over 10 minutes.

3. Mixing continued for 20 minutes.

4. Addition of EHBC resin carried over 10 minutes.

5. Addition of EHBM resin carried over 20 minutes.

6. SBP2 was added.

7. Mixing continued for further 50 minutes.

Total mixing time = 2 hrs.

A 23 micron layer of adhesive was spread onto a 25 micron polyurethane film using a conventional adhesive spreading tunnel and the film cut into surgical drapes. The adhesive weight was approximately 30 grams per square metre.

Various physical and chemical tests were conducted in the samples but no significant differences in physical properties (e.g. gas and moisture permeability, adhesion, and tensile strength) were noted. The samples incorporating SSD also withstood ageing and sterilization treatments to a similar extent to the control sample.

The samples were then subject to microbiological evaluation with respect to a variety of bacterial challenges.

Samples of drapes, after ethylene oxide sterilisation, were tested by the zone diffusion technique. Discs of Opsite were placed with the adhesive down on neomycin assay agar plates, preseeding with challenge organisms. After incubation, the plates were examined and zones of inhibited growth around the samples measured.

The diameter of the discs was 10 mm, and the diameter of the inhibited zones around (and including) the discs was as follows:

Content of S.S.D.%	Zone diameter (mm) including Opsite 0	5	10
Test organism			
Staph.aureus	11.9	13	15.2
Ps.aeuruginosa	no zone	I	13.8
Eschericia coli	no zone	13	14
Candida albicans	no zone	I	I
Bacillus subtilis	no zone	I	15.7

I No zone around dressing but growth inhibited beneath samples.

CLAIMS

1. An adhesive-coated sheet material which is liquid-impervious but has a high moisture vapour permeability whereby it is suitable as a wound or burn dressing, or surgical drape, or like wound-covering material, wherein the adhesive coating has disseminated throughout its mass an amount of an antibacterial material sufficient to kill bacteria in the wound and surrounding covered skin area.

2. A sheet material according to claim 1 wherein the antibacterial material is a finely divided solid.

3. A sheet material as claimed in claim 2 in which the solid contains metal ions.

4. A sheet material as claimed in claim 3 in which the metal ion is silver ion.

5. A sheet material as claimed in claim 4 in which the antibacterial is silver sulphadiazine.

6. A sheet material as claimed in any one of claims 1 to 5 in which from 1 to 25% by weight of the antibacterial is utilised based on the weight of adhesive.

7. A sheet material as claimed in claim 6 in which from 5 to 15% by weight is utilized.

8. A sheet material as claimed in any one preceding

claim 2 to 7 in which the majority of the finely divided particles are less than five microns in diameter.

9. A sheet material as claimed in any one of claims 1 to 8 in which the polymer is polyurethane up to 75 microns in thickness .

10. A sheet material as claimed in any one of claims 1 to 9 in which the adhesive is a layer of a polyvinyl ether up to 75 microns in thickness.

11. A sheet material as claimed in claim 9 and 10 in which each layer is up to 30 microns in thickness.

12. A sheet material as claimed in any one preceding claim in combination with a peelable release layer on the adhesive face, to be removed prior to use.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 79/00188

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[3]: A 61 L 15/06

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System [5]	Classification Symbols
Int.Cl.[3]	A 61 L 15/06; A 61 L 15/03

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO SE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	FR, A, 2012584, published March 20, 1970, see page 16, lines 21-24; page 31, claims 1,6; page 32, claims 17,18; page 35, claims 35,41; page 37, claims 56 ,63; Smith & Nephew	1-12
	--	
	FR, A, 2368962, published May 5, 1978, see page 1, lines 1-14; page 10, claim 1, Merck	1,9
	--	
	US, A, 3969498, published July 13, 1976, see column 2, lines 52-60; column 3, examples 3 and 4, P.N. Catania	2-5
	--	
	US, A, 3598123, published August 10, 1971, see column 3, lines 57-59; column 7, claim 1, A. Zaffaroni	1
	--	
	FR, A, 2184498, published December 12, 1973, see page 2, lines 1,2; page 4, claim 7, L.H.D.	1
	--	
	US, A, 2427022, published November 7, 1942, see column 3, lines 18-23; W.R. Russ	1
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	./.	

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
21st February 1980	3rd March 1980
International Searching Authority [1]	**Signature of Authorized Officer [20]**
European Patent Office	G.L.M. KRUYDENBERG

Form PCT/ISA/210 (second sheet) (October 1977)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

DE, C, 685805, published April 18,1939, see page 1, lines 10-16, DuPont — 1

DE, A, 1925348, published November 26, 1969, see page 6, claim 5, Schering — 1

A FR, A, 811222, published September 23, 1936 see page 2, lines 64-66, I.G. Farbenindustrie — 1,10

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.